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EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/731,542	BEHBOODI ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3/05;3/06* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-35 are pending and under consideration in the instant office action.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. [1] as follows:

It is noted that this application appears to claim subject matter disclosed in prior US Provisional Application No. 60/432,163, filed 12/10/2002. A reference to the prior application must be inserted as the first sentence(s) of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e), 120, 121, or 365(c). See 37 CFR 1.78(a).

For benefit claims under 35 U.S.C. 120, 121, or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference to the prior application must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The

Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

Information Disclosure Statement

Applicants' IDS, filed 03/03/2005 and 03/06/2006, have been considered.

Claim Objections

Claim 1 is objected to because of the following informalities: Claim 1 appears to be incomplete as the final step listed, step vii, ends with "...to produce a second embryo; and". The claim will be examined as though it ends at the word "embryo" in line 16. Appropriate correction is required.

Claims 20,21 and 35 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 20,21 and 35, which depend from method claims, are directed to a product. The claims should be written in independent form as product by process claims.

Claim 21 is objected to because of the following informalities: The phrase "further comprising wherein" is grammatically improper. Furthermore, the phrase "as a result of said

nuclear transfer procedure" is redundant because the claim is drawn to "The resultant offspring". Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 20 and 35 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 20 and 35 are directed to offspring of the method of cloning a non-human mammal of claims 1 and claims 24 or 29, respectively. Such an offspring is indistinguishable from the mammal from which it is derived and is also indistinguishable from any other mammal of the same species. As such, the claims read on a product of nature, which is non-statutory subject matter.

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20 and 22-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for cloning a non-primate mammal through a nuclear transfer process using non-primate mammalian cells as a source of donor nuclei

comprising an additional recloning step using a cell from a first nuclear transfer embryo, said method wherein it further comprises genetically modifying a fibroblast cell in vitro prior to the initial nuclear transfer, and a non-primate mammal made by the method wherein when the mammal is transgenic and the transgene is expressed, does not reasonably provide enablement for the claimed method in a primate species, for the claimed method wherein a transgene is introduced into non-fibroblast somatic cells in culture, or for a transgenic non-primate mammal wherein the transgene is not expressed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the

breadth of the claims. While all of these factors are considered, a sufficient amount for a prima facie case are discussed below.

The claimed invention is directed to methods for producing a non-human mammal by transferring the nucleus of a differentiated mammalian cell into an enucleated oocyte and simultaneously fusing and activating the resulting cell couplet, culturing the resulting first embryo until at least the 2-cell stage and using at least one cell from said first embryo as a donor cell for the nuclear transfer to form a second embryo. Claim 19 is drawn to genetic modification of the donor nucleus prior to insertion into an enucleated oocyte. Claims 20,21 and 35 are drawn to offspring made by the claimed method. It is noted that claim 1 is unclear, and rejected under 35 USC 112, 2nd paragraph (below), because method steps (vi) and (vii) recite that transgenic embryos are formed. However, the preamble and step (i) fail to require the presence of a transgene and no method step introduces a transgene. Therefore, for the purpose of examining the claims under the enablement requirement, the claim is interpreted as reading on a method of cloning a transgenic non-human mammal using a donor cell from a transgenic mammal (page 10, paragraph 0031) as well as using a non-transgenic mammal as a source of the differentiated donor cell of step (i) followed by in vitro transformation (pages 16-17, paragraph 0049).

1) Claims 1-7,10-14, and 16-35 are broad in that they encompass methods of cloning primate mammals or the resultant offspring or embryo. The specification teaches applying the claimed method to goats, which are non-primate, ungulate mammals. The specification fails to provide any guidance with respect to cloning primates. The primate embodiments of the claims are not enabled because of the art-recognized inability to clone primates. Vogel [**Science**, 300:226-227 (2003)] state that Rhesus monkey nuclear transfer (NT)-generated embryos seemed

normal at their early stages but were unable to develop further when implanted into a surrogate mother. This was because the cells had the wrong number of chromosomes, and that this aneuploidy resulted in the abortion of the fetus. This was found to also be the case with human NT embryos. See p. 225. Simerly et al. [**Science**, 300:297 (2003)] state that, "Primate NT appears to be challenged by stricter molecular requirements than in other animals ... With current approaches, NT to produce embryonic stem cells in nonhuman primates may prove difficult - and reproductive cloning unachievable." See p. 297, 3rd column, last sentence. As the state of the art evidences, NT in primates is unpredictable, and the instant specification fails to provide teachings to show that primate NT using the claimed methods would result in pluripotent mammalian cells, it would have required undue experimentation for one of skill in the art to make and use the claimed invention.

2) Claim 19 requires genetic modification, including gene targeting by homologous recombination of the donor nuclear genome prior to insertion of the donor nucleus into the recipient cell (see page 16-17, paragraph 0049). The claims encompass in vitro genetic modification of a cell after isolation from a mammal, just prior to insertion into the oocyte recipient. Similarly, claim 1, if interpreted as being drawn to a method of cloning a non-human mammal that results in formation of a transgenic embryo (as recited at steps iv and vii of claim 1) using a non-transgenic donor cell (step i), also reads on genetic modification of a somatic donor cell in vitro (see rejection under 35 USC 112, 2nd paragraph below). Thus, claims 1 and 19 (and dependent claims) encompass non-enabled embodiments requiring introduction of a

transgene into a differentiated, non-fibroblast somatic cell in vitro, prior to introduction of said cell of nucleus into an enucleated oocyte.

The specification teaches making transgenic goats using the claimed methods by using fetal fibroblast cells derived from an established transgenic CFF6 line of goats as nuclear donors (see page 11, paragraph [0033]). The specification does not teach in vitro transformation of fetal or adult somatic cells immediately prior to nuclear transfer as encompassed by the claims. The art at the time of filing held that genetic modification of somatic cells in culture was an underdeveloped art.

At the time of filing, the only somatic cell type that could be genetically modified in culture to form an animal was a fibroblast [Schnieke et al. 1997, **Science**, 278:2130-2133]. Thomson et al. [**Reprod. Supp.**, 61:495-508, 2003] review the state of the art of gene targeting in somatic cells for use in nuclear transfer methodologies and state that procedures to enhance the lifespan of targeted somatic cells in vitro are needed. In particular, Thomson states that premature senescence often occurs, which makes it difficult to confirm a targeting event in somatic cells and that cloning efficiency has been negatively correlated with passage number. See p. 501. The inefficiency and unpredictability of homologous recombination in somatic cells is supported by Polejaeva and Campbell [**Theriogenology**, 53:117-126, 2000] who teach that gene targeting in somatic cells is unpredictable because of the lower frequency of homologous recombination than ES cells, and a finite capacity for number of cell divisions. Polejaeva and Campbell further discuss specific criteria for more efficient somatic cell gene targeting, such as the ability of the cells to have a high single cell-cell cloning efficiency because during drug selection, the cells must be able to expand into clonal cultures. However, they note that human

dermal fibroblasts are not able to proliferate under regular culture conditions, and thus, optimization of culture conditions must be attained for success in somatic cell gene targeting. See p. 120-121. Denning taught that primary cells have limited proliferation capacity and any genetic modifications and nuclear transfer must be accomplished prior to senescence [**Cloning and Stem Cells**, 3:221-231, 2001, specifically refer to page 222, col. 1, lines 5-8]. In a study of sheep and goat primary somatic cells, Denning found that of primary somatic cells, fibroblasts were the only cells that either grew at all from the primary cell source or has sufficient population doublings for the selection required in targeted gene transfer. Sheep primary cell cultures primarily were composed of fibroblasts after the third passage or about 12 doublings (Denning, page 224, col. 2, lines 11-13). In a similar analysis of pig primary cultures, fibroblasts, as in the sheep study, became the predominant cell-type after three passages, but, unlike sheep, pig fibroblasts underwent a crisis after 40 population doublings and had an unstable karyotype (Denning, page 224, col. 2, parag. 4 line 4 to page 225, col. 1, line 8). Additional studies of cell cultures prepared from fetal pig organs (gut, kidney, lung and mesonephros) showed that these cells senesced or entered crisis after even fewer doublings than the fibroblast cultures (page 225, col. 1-2, bridg. sent.). The art further taught at the time of filing, that the even if sufficient population doublings could be achieved for selection, many of the pure sheep targeted clones senesced before they could be expanded for nuclear transfer, meaning that targeting frequency was lower than expected (page 228, col. 1-2, bridg. sent.). Similar experiments in pigs demonstrated that all the clones senesced, and no targeted cells for nuclear transfer were obtained. Clearly, the art supports the unpredictability and underdeveloped nature of gene targeting using any somatic cell type for use in nuclear transfer methodologies, and more

specifically, that candidate somatic cells that would be used for gene targeting must be able to survive multiple rounds of cell division, selection and overcome senescence. The specification fails to provide teachings or guidance for utilizing any somatic cell for gene targeting which would be further used in nuclear transfer methods. While the state of the art supports that particular cell types, such as fetal fibroblasts, can be used in the claimed methods, specific guidance must be provided to enable the breadth of the claims.

Clearly, the art has established unpredictability in the gene-targeting and random introduction of transgenes to any somatic cell type for use in nuclear transfer methodologies, and has acknowledged that candidate somatic cells that would be used for recombinant DNA technology must be able to survive multiple rounds of cell division, selection and overcome senescence. Therefore, in addition to the aspects set forth above, with respect to the aspect of the claimed invention involving genetic modification of a donor cell in vitro, the specification is further not enabling for making a transgenic nuclear transfer mammal by any means other than use of a fetal fibroblast cell.

To the extent that the claims read on a transgenic non-human mammal, claim 20 does not require expression of the transgene. The specification teaches cloning a transgenic goat expressing a desired protein in the milk as a means of producing large quantities of the protein. The specification does not teach how one of skill in the art would use a transgenic non-human mammal that does not express the transgene. It would require undue experimentation to determine how to use the claimed transgenic mammals wherein the transgene is not expressed.

Claim 21 and 24-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 21 is drawn to an offspring of the method of cloning a non-human mammal (claim 19) wherein the offspring created by the method is chimeric. The method, as claimed, results in a non-chimeric animal. There are no method steps in the claim, or in the base claim, that would lead to chimerism. Furthermore, chimeras are highly variable because tissue distribution in a chimera cannot be controlled or be predictably reproduced. Therefore, one of skill in the art at the time of filing would not know how to make any chimera as claimed and would not know how to use the chimera. It would require undue experimentation to determine how to make and use a chimeric offspring as claimed.

Claims 24-35 are not enabled because claims 24 and 29 require use of an oocyte as a nuclear donor (see rejection under 35 USC 112, 2nd paragraph below). Oocytes are not differentiated cells as required by the claims and the art and the specification fail to provide guidance as to how to carry out nuclear transfer using a haploid oocyte as a nuclear donor.

To the extent that the claims read on a transgenic non-human mammal, claims 21 and 35 do not require expression of the transgene. The specification teaches cloning a transgenic goat expressing a desired protein in the milk as a means of producing large quantities of the protein. The specification does not teach how one of skill in the art would use a transgenic non-human mammal that does not express the transgene. It would require undue experimentation to determine how to use the claimed transgenic mammals wherein the transgene is not expressed.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is unclear because it is drawn to a method of cloning a non-human mammal, which includes non-transgenic mammals. However, steps (vi) and (vii) recite formation of transgenic embryos without any steps of introducing a transgene required by the claim. It is unclear whether the claim is intended to be directed to a method of cloning a transgenic non-human mammal, or to a method of introducing a transgene to make a transgenic mammal by nuclear transfer but is missing method steps involving introduction of the transgene to the nuclear donor, or if the embryos in steps (vi) and (vii) are not truly intended to be transgenic. Claims 2-35 depend from claim 1.

Claim 1 recites the limitation "the desired differentiated cell or cell nucleus" in line 8. There is insufficient antecedent basis for this limitation in the claim. Step (i), at line 3 of the claim, refers to "cells" in the plural and it is unclear if the "cell" of line 8 is referring back to the "cells" of line 3 or some other cell. It is unclear also if "the desired differentiated cell" of line 8 is meant to be a desired, single cell of the set of "cells" of line 3 that was chosen as "desired" by a method step omitted from the claim. Claims 2-35 depend from claim 1.

Claim 1 recites the limitation "the cell couplet" in line 10. There is insufficient antecedent basis for this limitation in the claim. The cell couplet is presumed, for the purpose of further examination, to be the structure formed by step (iv) of claim 1. Claims 2-35 depend from claim 1.

Claim 1 is incomplete as written. The preamble of the claim is directed to a method for making a non-human mammal. However, the claims are incomplete because the method steps do not relate back to the preamble in a positive process. The method steps of the claims result in a non-human fetus, not a mammal, which is interpreted as being a live-born animal. Appropriate correction is required. Claims 2-35 depend from claim 1.

Claim 1 is unclear because they are drawn to a method of cloning a non-human mammal but recite use of any mammalian species of donor cell, including human donor cells. Thus, the method steps are not commensurate in scope with the preamble, making it unclear what is being claimed. Claims 2-35 depend from claim 1.

Claim 17 recites the limitation "the fetus" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 19 is unclear because it depends from claim 1, which is drawn to a method of cloning a non-human mammal, which requires that the product made by the method be genetically identical to the source of the donor nucleus, i.e. a clone. However, claim 19 appears to be directed to in vitro genetic modification of the donor cell prior to nuclear transfer after isolation from the donor animal. The product made by such a method would differ genetically from the "parent" and therefore would not be a clone. As such, claim 19 fails to relate back to the preamble of the parent claim. Claims 20 and 21 depend from claim 19.

Claims 20,21 and 35 recite the limitation "The resultant offspring" in line 1. There is insufficient antecedent basis for this limitation in the claim or base claim. To make an offspring requires birth, which is not a step required by the claims.

Claims 22 and 23 recite the limitation "the cloning protocol" in line 1. There is insufficient antecedent basis for this limitation in the claim. The claims are drawn to use of cytochalasin B in the cloning protocol (claim 22) or to the lack of use of cytochalasin B in the cloning protocol (claim 23). It is not clear what steps of the base claim 1 is considered the "cloning protocol". It could refer to all steps of the claim or just to those directly involving the combination of a nucleus with a cytoplast. The specification teaches use of cytochalasin B for two independent steps, in enucleation of the oocyte and in introduction of the donor nucleus to the cytoplast. The former requires use of cytochalasin B and the latter use is optional (see page 13 of the specification). The art has taught use of cytochalasin B in enucleation (for example see Campbell, 1994) but has taught that in some cases while used in enucleation, it is preferably omitted from steps of introducing the donor nucleus (for example, see Park et al., 1994, IDS). Therefore, for the purpose of examination under 35 USC 102 and 103, see below, because the specification and the art indicate necessity of cytochalasin B in enucleation but not in introduction of donor nucleus, the claims are interpreted to refer to the use of cytochalasin B in the "cloning protocol" as it relates to the step of introducing the donor nucleus.

Claims 24 and 29 are wholly unclear. The claims limit the differentiated mammalian cells used as a source of donor nuclei of claim 1 and 29, respectively, to that from an in vitro (claim 24) or in vivo (claim 29) matured oocyte. Oocytes are not differentiated cells and are not known in the art or described in the instant specification to be nuclear donors. Thus, it is unclear what is

intended to be claimed. Claims 25-28 depend from claim 24. Claims 26-35 depend from claim 29.

Claim 17 recites the limitation "the fetus" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1) Claims 20 and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Wilmut (1997, IDS).

Claim 20 is drawn to the resultant offspring of the methods of claim 1 or 19. As set forth above under 35 USC 112, 2nd paragraph, it is unclear whether claim 1 is drawn to a method of making a transgenic non-human mammal, a non-transgenic non-human mammal or both. The preamble does not indicate the presence of a transgene and the method steps do not require introduction of a transgene. As such, to the extent that the claim 1 reads on a method of cloning a non-transgenic non-human mammal, the following rejection is necessitated. While claim 35 is unclear due to the lack of clarity of independent claim 24, it appears to be drawn to a non-human mammal resulting from a nuclear transfer method and is included in this rejection to the extent that it is considered a product by process claim wherein process of making is given little patentable weight.

Claim 20 is drawn to the resultant offspring of the method of claim 1, which is a method of cloning a non-human mammal. Claim 35 is drawn to the resultant offspring of the method of

claim 24, which is a method of cloning a non-human mammal. These claims are interpreted as product by process claims.

Wilmut *et al.* taught a wild-type female ewe (page 811, col. 1, lines 9-10).

A mammal obtained by the method of claim 1 would not differ structurally from a mammal of the same species obtained through any other method, including natural mating and birth. Patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it that is recited in the claims. See In re Thorpe, 227 USPQ 964 (Fed. Cir. 1985). Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). Further, see MPEP §2113, "Even though product-by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process."

Therefore, Wilmut taught all of the limitations of claims 20 and 35.

2) Claims 20 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Mansour [1993, **Development**, 117:13-28].

Claim 20 is drawn to the resultant offspring of the methods of claim 1 or 19. Claim 21 is drawn to the resultant offspring of the method claim 19, which is a method of cloning resulting in introduction of a transgene into a non-human mammal.

Claims 20 and 21 are drawn to the resultant offspring of the method of claim 19, which is a method of cloning a non-human mammal that results in a transgenic mammal. Claim 21 requires that the offspring be chimeric. These are interpreted as a product by process claims.

Mansour taught a method of making genetically modified mice that results in an intermediate product of chimeric, transgenic mice (page 15, col. 2, paragraph 3) as well as a final product of non-chimeric, transgenic mice (page 15, col. 2, paragraphs 3-4).

A mammal obtained by the method of claim 19 would not differ structurally from a mammal of the same species obtained through any other method, including natural mating and birth. Patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it that is recited in the claims. See In re Thorpe, 227 USPQ 964 (Fed. Cir. 1985). Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the

PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). Further, see MPEP §2113, "Even though product-by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process."

Therefore, Mansour taught all of the limitations of claims 20 and 21.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1) Claims 1,2,5-9,11,13,17,19, 20 and 22 are rejected under 35 U.S.C. 103(a) as being obvious over Schnieke et al. (1997, **Science**, 278:2130-3) as evidenced by Wilmut (1997, IDS), by Campbell (1996, IDS) and by Campbell [1994, **Biology of Reproduction**, 50:1385-1393], in view of Zakhartchenko (1999, IDS) or Wells (1999, IDS).

Claim 1 is drawn to a method of cloning a non-human mammal comprising transferring the nucleus of a differentiated mammalian cell into an enucleated oocyte of the same species, simultaneously activating the resulting cell couplet, culturing the embryo until it reaches at least the two-cell stage and using a cell from said embryo to form a second embryo through a second round of nuclear transfer. Claim 2 requires that the donor cell be derived from mesoderm. Claims 5 and 6 requires that the donor cell be from fetal tissue or cells and claim 7 requires it be a fibroblast while claim 11 is drawn to additional specific cell types for the donor cell. Claims 8 and 9 are drawn to specific mammalian species. Claim 13 requires in vivo oocyte maturation. Claim 17 requires development of the fetus into an offspring. Claim 19 requires a transgenesis step. Claim 20 is drawn to an offspring made by the claimed method and claim 22 requires use of cytochalasin B in the cloning protocol.

Schnieke taught cloning of ovine, an ungulate, by nuclear transfer using quiescent fetal fibroblasts, which are differentiated, mesodermally derived cells, (page 2130, col. 3, paragraph 4). Schnieke transformed the fibroblasts with a transgene, which is required by claim 19 and fulfills the transgenic recitation in steps (vi) and (vii) of claim 1. Schneike obtained oocytes from the same species, sheep, incubated them in medium containing cytochalasinB (claim 22) prior to enucleation (taught by reference at Schnieke page 2131, col. 3, paragraph 3 to Campbell, 1994,

page 1386, col. 1, paragraph 5 through Campbell, 1996). Donor cells were transferred into the oocyte and fusion and activation were simultaneously induced by electrical shock pulses (taught by reference at page 2131, col. 3, paragraph 3 and Wilmut, page 813, col. 1, paragraph 3). It is noted that Schnieke taught many of the claim limitations by reference to which can be found at page 813 of Wilmut and also, by further reference to Campbell, 1996 that references Campbell, 1994. It is also noted that the oocytes were recovered at metaphase II from the oviducts (see Campbell, 1994, page 1386, col. 1), which are in vivo matured (claim 13). Schnieke did not teach a re-cloning step as required by step (vii) of claim 1.

However, both Zakhartchenko (1999) and Wells (1999) taught growing a first nuclear transfer embryo and using morulae from the first cloning round (see paragraph bridging pages 326-327 of Zakhartchenko and page 998, col. 2, paragraph 4 of Wells). Both Zakhartchenko and Wells each taught increased developmental capacity and cloning efficiency using a recloning step (see Zakhartchenko, page 326, col. 1, paragraph 2 and page 330, col. 1, paragraph 4; see also Wells, page 999, col. 2, paragraph 5).

It would have been obvious for one of skill in the art at the time of filing to combine the teachings of nuclear transfer in cloning a non-human mammal of Schnieke with those of wither Zakhartchenko or Wells, adding a recloning step. One would have been motivated to add a recloning step because both Zakhartchenko and Wells taught that greater efficiency of cloning resulting in live birth occurs when a recloning step is used.

One would have a reasonable expectation of success in combining the above teachings because the techniques necessary for the recloning step were known and are merely repetition of the steps taught by Schnieke.

Thus, the claimed invention, as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

2) Claims 3,4,10,12,14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schnieke (1997,) as evidenced by Wilmut (1997, IDS), by Campbell (1996, IDS) and by Campbell (1994), in view of Zakhartchenko (1999, IDS) or Wells (1999, IDS) as applied to claims 1,2,5-9,11,13,17,19, 20 and 22 above, and further in view of Campbell (WO 00/42174, published 20 July 2000).

As set forth above, Schnieke taught a method of cloning a sheep using fetal fibroblast cells.

Schnieke did not teach using adult cells (claim 10), ectodermally or endodermally derived cells (claims 3 and 4) or the cells from any of the organs listed in claim 12, as a nuclear donor. Schnieke did not teach use of in vitro maturation of oocytes (claim 14) or applying the cloning methods to rodent species as required by claim 15.

However, Campbell taught using any cell population from any stage in the life of an animal (see page 3, lines 25-29, and page 10, line 20-page 11, line 6). Campbell also taught that oocytes could be matured in vitro (page 13, lines 20-22). Furthermore, Campbell taught applying the methods of cloning to ungulate as well as rodent species (paragraph bridging page 3-4).

It would have been obvious at the time of filing to combine the methods of Schnieke and of Zakhartchenko or Wells with the teachings of Campbell using cells derived from an adult mammal to make a cloned mammal by nuclear transfer, including rodent species using in vitro matured oocytes. One of skill in the art at the time of filing would have been motivated to use a

cell derived from an adult mammal to avoid having to generate a fetus as well as to clone an adult, rather than cloning a fetal offspring of a desired adult. Use of a somatic cell to clone an adult would allow for formation of genetically identical tissues that could be use to treat diseases, disorder or injury in a mammal. One of skill in the art would have been motivated to use the claimed methods in rodent species because the method provides a means of introducing transgenes into rodent species that are otherwise not amenable to transgenesis. One of skill in the art would have been motivated to substitute in vitro matured oocytes for in vivo matured oocytes because in vitro maturation would allow for harvesting of large numbers of immature oocytes from an ovary of a pig over hormonally inducing in vivo maturation and release of oocytes from pigs in vivo. In vitro maturation also allows for collection of oocytes post-mortem.

To the extent that the claims read on cloning a transgenic mammal, as opposed to introducing a transgene into donor cells in culture, one would have a reasonable expectation of success in combining the methods of Schnieke with those of Campbell in using adult cells as nuclear donors because both adult and fetal cells are differentiated, somatic cells. Furthermore, at the time of filing, it was becoming more routine in the art to use adult cells as taught by Campbell and to perform nuclear transfer in both livestock and rodent mammalian species.

Thus, the claimed invention, as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

3) Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Schnieke (1997) as evidenced by Wilmut (1997, IDS), by Campbell (1996, IDS) and by Campbell (1994)

in view of Zakhartchenko (1999, IDS) or Wells (1999, IDS) as applied to claims 1,2,5-9,11,13,17,19, 20 and 22 above, and further in view of Cibelli, (1998, IDS).

As set forth above, Schnieke in view of Zakhartchenko or Wells taught a method of cloning a sheep using quiescent fetal fibroblast cells.

Schnieke did not teach use of non-quiescent cells as nuclear donors.

However, Cibelli taught use of non-quiescent fetal fibroblasts as nuclear donors to clone calves. Cibelli taught that active cell division is an indication of a relatively undifferentiated state (page 1256, col. 3, paragraph 1).

It would have been obvious at the time of filing to combine the methods of Schnieke and if Zakhartchenko or Wells with the teachings of Cibelli using non-quiescent cells as nuclear donor. One of skill in the art at the time of filing would have been motivated to use a non-quiescent cell as a nuclear donor because Cibelli taught that other research had shown that the cell cycle stage of the donor cell affects the extent of development of an embryo after nuclear transfer (page 1256, col. 2, paragraph 2) and obtained a high efficiency of cloning using dividing cells.

One would have a reasonable expectation of success in combining the methods of Schnieke and of Zakhartchenko or Wells with those of Cibelli because Cibelli demonstrated that dividing cells have the capacity to be reprogrammed to totipotency and are capable of generating a viable mammal.

Thus, the claimed invention, as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

4) Claims 14 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schnieke (1997), as evidenced by Wilmut (1997, IDS), by Campbell (1996, IDS) and by Campbell (1994), in view of Zakhartchenko (1999, IDS) or Wells (1999, IDS) as applied to claims 1,2,5-9,11,13,17,19, 20 and 22 above, and further in view of DeSousa (US 6,548,741, published 12/06/2001 as US 2001/0049829)

As set forth above, Schnieke taught a method of cloning a sheep using in vivo matured oocytes. Schnieke did not teach use of in vitro matured oocytes. However, DeSousa taught use of in vitro matured oocytes for nuclear transfer in pigs (col. 4, line 60-col. 5, line 4 and claim 1). DeSousa taught that the oocytes should be matured in vitro for about 42 to 46 hours prior to enucleation, which is within the claimed 10 to 60 hours as claimed (claim 18).

It would have been obvious for one of skill in the art at the time of filing to use in vitro matured oocytes as taught by DeSousa in the methods of Schnieke. One of skill in the art would have been motivated to substitute in vitro matured oocytes for in vivo matured oocytes because in vitro maturation would allow for harvesting of large numbers of immature oocytes from an ovary of a pig over hormonally inducing in vivo maturation and release of oocytes from pigs in vivo. In vitro maturation also allows for collection of oocytes post-mortem (see DeSousa, col. 9, lines 25-30).

One would have a reasonable expectation of success in combining the methods of Schnieke with those of DeSousa because DeSousa demonstrated the success and capacity of in vitro matured oocytes to support parthenogenic activation to the same degree as in vivo matured oocytes.

Thus, the claimed invention, as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

5) Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Schnieke (1997) as evidenced by Wilmut (1997, IDS), by Campbell (1996, IDS) and by Campbell (1994), in view of Zakhartchenko (1999, IDS) or Wells (1999, IDS) as applied to claims 1,2,5-9,11,13,17 19, 20 and 22 above, and further in view of Park, (2001,IDS).

As set forth above under 35 USC 112, 2nd paragraph, claim 23 is unclear as to what is referred to as the "cloning protocol" and the claim is interpreted as requiring omission of cytochalasin B from the method of introducing a donor nucleus into an enucleated oocyte.

As set forth above, Schnieke taught a method of cloning by nuclear transfer using cytochalasin B in the protocol. Schnieke did not teach cloning by nuclear transfer without use of cytochalasin B.

However, Park et al taught that cytochalasin B is not necessary, and is contraindicated for methods of introducing a donor nucleus into a pig oocyte (paragraph bridging pages 1683-1684).

One of skill in the art would have been motivated to apply the teachings of Park to those of Schnieke and remove cytochalasin B from the activation protocol because Park taught that cytochalasin B is not necessary and can harm the integrity of the donor cells. One would have been motivated to remove cytochalasin B from the protocol because it is not necessary and to maintain donor cell integrity.

One of skill in the art would have a reasonable expectation of success in combining the methods of Schnieke with those of Park because Park demonstrated that cytochalasin B is not

necessary in manipulating donor cells and that removal does not inhibit the success of nuclear transfer.

Thus, the claimed invention, as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Valarie Bertoglio
Examiner
Art Unit 1632